Structure and Reactivity of Lithium Diisopropylamide Solvated by Polyamines: Evidence of Monomer- and Dimer-Based Dehydrohalogenations

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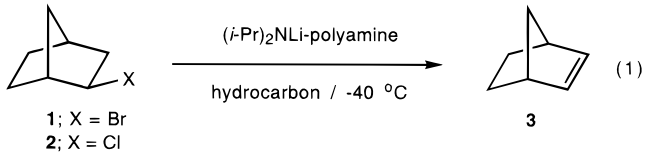
Abstract: ^{6}Li and ^{15}N NMR spectroscopic studies show that hexane solutions of LDA containing <1.0 equiv of *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PMDTA) per lithium contain a mixture of unsolvated LDA oligomers, monosolvated open dimer, and monosolvated monomer. At >1.0 equiv of PMDTA per lithium, monomer is the dominant species. Addition of PMDTA to LDA in toluene affords open dimer at low [PMDTA] and a mixture of LDA monomer and benzyllithium (resulting from toluene deprotonation) at high [PMDTA]. The results are compared and contrasted with previous investigations of LDA solvated by *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and (±)-*trans*-*N*,*N*,*N*′,*N*′-tetramethylcyclohexanediamine (TMCDA). The reactivities of LDA solvated by TMEDA, TMCDA, and PMDTA were probed by investigating the dehydrohalogenation of (±)-2-*exo*-bromonorbornane. All three ligands afford qualitatively similar behavior: (1) a maximum reactivity at low ligand concentrations ascribed to monosolvated LDA dimers and (2) ligand-concentration-independent rates at high ligand concentrations ascribed to monosolvated LDA monomers. Structure and rate differences in hexane and toluene solutions are noted.

Introduction

There is a considerable body of literature describing reactions of organolithium reagents and related lithium salts.[1−3] From the relatively small number of structural and rate studies and enormous number of empirical observations have emerged a series of dictums that describe organolithium reactivities. Three that have been reiterated frequently are as follows: (1) strong donor solvents (ligands) promote conversion of aggregates to monomers or ion pairs; (2) monomers are more reactive than aggregates; and (3) strong donor solvents enhance reactivity. In fact, any one of these is often implied to be a corollary of the other two. Over the past few years we have challenged these ideas as simplistic and, at times, fundamentally flawed.[3]

We describe herein investigations of lithium diisopropylamide (LDA)[4,5] solvated by *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA),[3] (±)-*trans*-*N*,*N*,*N*′,*N*′-tetramethylcyclohexanediamine (TMCDA),[6−10] and *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PMDTA).[6−10] NMR spectroscopic studies reveal monomeric and dimeric LDA-PMDTA solvates as well as several important consequences of using toluene as the "inert" cosolvent. Rate studies of an LDA-mediated dehydrohalogenation (eq 1)[10] reveal competing elimination mechanisms based



(1)

upon LDA monomers as well as evidence of dimer-based pathways as first proposed by Schlosser and co-workers.[11,12] Contrary to conventional wisdom, the polyamines afford optimum elimination rates via the putative dimer-based pathways.

Results

Solution Structures: LDA/PMDTA. We previously reported the structures of LDA-solvated TMEDA and TMCDA

(1) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. For extensive additional references to general reviews of organolithium chemistry, see ref 2.

(2) Reviews of lithium amide structural studies: (a) Gregory, K.; Schleyer, P. v. R.; Snaith, R. *Adv. Inorg. Chem.* **1991**, *37*, 47. (b) Mulvey, R. E. *Chem. Soc. Rev.* **1991**, *20*, 167. (c) Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227.

(3) Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227.

(4) Lithium dialkylamides are important reagents in synthetic organic chemistry. For extensive leading references, see refs 7−10.

(5) For leading references to other mechanistic, spectroscopic, and crystallographic studies of LDA, see ref 8.

(6) For leading references to TMCDA and PMDTA in organolithium chemistry, see refs 7−9.

(7) For previous spectroscopic investigations of lithium amides solvated by polydentate ligands, see: Lucht, B. L.; Bernstein, M. P.; Remenar, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 10707. Also, see refs 8 and 9.

(8) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567.

(9) Remenar, J. F.; Lucht, B. L.; Kruglyak, D.; Romesberg, F. E.; Gilchrist, J. H.; Collum, D. B. *J. Org. Chem.* **1997**, *62*, 5748.

(10) The LDA-mediated elimination of (±)-2-*exo*-bromonorbornane has been studied previously: Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5573.

(11) Matsuda, H.; Hamatani, T.; Matsubara, S.; Schlosser, M. *Tetrahedron* **1988**, *44*, 2865.

(12) For selected applications and mechanistic investigations of lithium amide-mediated 1,2-eliminations, see: (a) Mass, R. J.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 1992. (b) Kopka, I. E.; Nowak, M. A.; Rathke, M. W. *Synth. Commun.* **1986**, *16*, 27. (c) Evans, K. L.; Prince, P.; Huang, E. T.; Boss, K. R.; Gandour, R. D. *Tetrahedron Lett.* **1990**, *31*, 6753. (d) Reisdorf, D.; Normant, H. *Organomet. Chem. Synth.* **1972**, *1*, 375.

(13) Bernstein, M. P.; Romesberg, F. E.; Fuller, D. J.; Harrison, A. T.; Williard, P. G.; Liu, Q. Y.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 5100.

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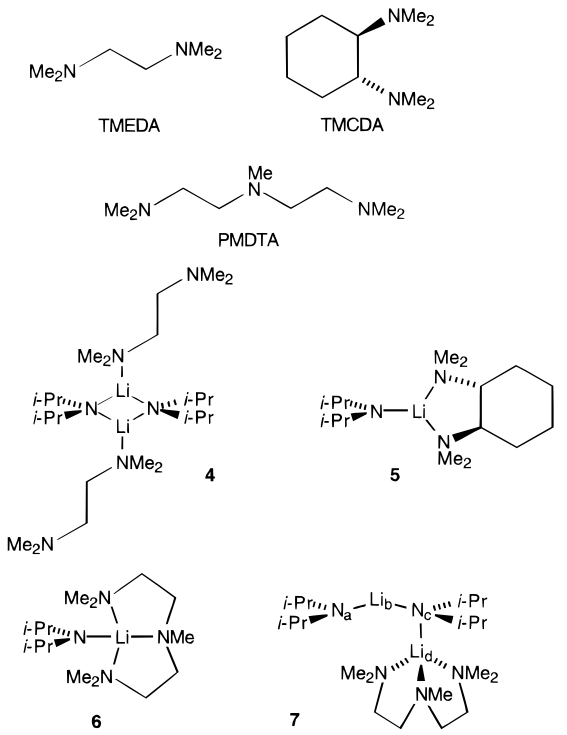
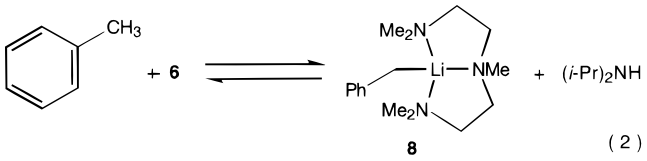
Chart 1



to be dimer **4** and monomer **5**, respectively.[8,13] The structure of LDA solvated by PMDTA has not been described.

Addition of 0.5 equiv of PMDTA (per Li) to 0.1 M solutions of [^{6}Li,^{15}N]LDA[14] in toluene affords substantial concentrations of open dimer **7**, unsolvated cyclic oligomers,[13,14] monomer **6**, and an impurity shown to be PMDTA-solvated benzyllithium **8** (Figure 1, eq 2). Monomer **6** and benzyllithium **8** are the



(2)

only observable forms at >1.0 equiv of PMDTA. Monomer **6** is characterized by a ^{6}Li doublet (δ 0.86 ppm, $^1J_{Li-N}$ = 8.5 Hz) and an ^{15}N triplet (δ 89.4 ppm, $^1J_{Li-N}$ = 8.1 Hz). The assignment of open dimer **7** also follows directly from the coupling patterns. The $N_a-Li_b-N_c-Li_d$ connectivity in **7** is readily discerned from a ^{6}Li doublet (Li_d, δ 0.19 ppm, $^1J_{Li-N}$ = 5.1 Hz), a ^{6}Li doublet-of-doublets (Li_b, δ 2.86 ppm, $^1J_{Li-N}$ = 10.3 and 5.4 Hz), an ^{15}N triplet (N_a, δ 99.7 ppm, $^1J_{Li-N}$ = 10.0 Hz), and an ^{15}N quintet (N_c, δ 75.7 ppm, $^1J_{Li-N}$ = 5.3 Hz).[15] The connectivities were confirmed by single-frequency decoupling.[16] The η^3 (tridentate)[8] rather than η^2 (bidentate)[17] PMDTA ligation in **6** and **7** is inferred from the dramatically different results obtained with TMEDA (see below).[13]

The assignment of the PMDTA-solvated benzyllithium (**8**) was elusive at first since literature pK_A's in other solvents[18]

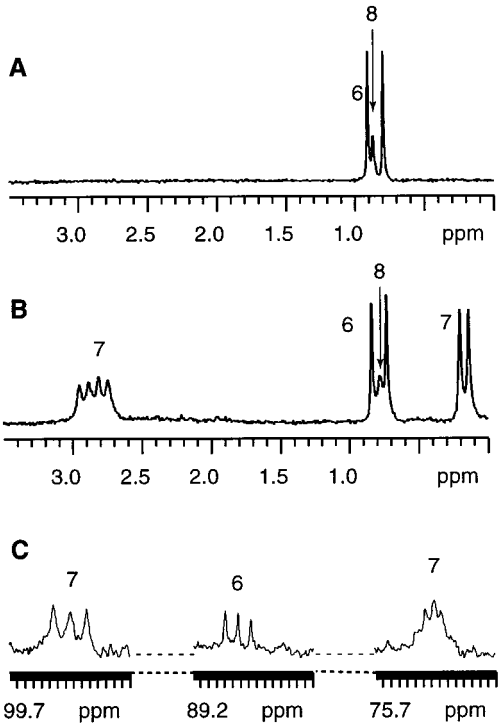


Figure 1. Representative NMR spectra of samples containing 0.10 M [^{6}Li,^{15}N]LDA in 2:1 toluene−pentane mixtures. (A) ^{6}Li NMR spectrum with 2.0 equiv of PMDTA at −95 °C; (B) ^{6}Li NMR spectrum with 0.5 equiv of PMDTA at −115 °C; (C) partial ^{15}N NMR spectrum with 0.5 equiv of PMDTA at −115 °C.

indicate that the benzyllithium concentrations would remain several orders of magnitude below detection limits. However, the ^{6}Li singlet at δ 0.85 ppm is observed only in toluene solutions of LDA/PMDTA, increases in proportion to the toluene concentration (using hexane cosolvent), and remains at constant intensity over a range of [PMDTA] (1.5−10 equiv per Li). The ^{15}N NMR spectra contained no new ^{15}N resonances, arguing against a new LDA-derived fragment. The ^{6}Li singlet appears substantially more slowly in toluene-d_8 than toluene, yet reaches the same maximum intensity. A compelling assignment of **8** came from the ^{13}C NMR spectrum of LDA/PMDTA in toluene. The three most readily observable aromatic carbon resonances at 159.7, 116.6, and 105.6 ppm are similar to those reported for related benzyllithium derivatives.[19] The ^{6}Li and ^{13}C NMR spectra of benzyllithium prepared independently from *n*-BuLi/PMDTA in toluene confirm the assignment. Last, addition of diisopropylamine to the toluene solution of benzyllithium/PMDTA affords a ^{6}Li spectrum that is indistinguishable from that derived from LDA/PMDTA in toluene.

Substantially different results emerge when hexane is used as the cosolvent. Addition of 0.5 equiv of PMDTA (per Li) to 0.1 M solutions of [^{6}Li,^{15}N]LDA in hexane affords unsolvated LDA cyclic oligomers, monomer **6**, and a partially solvated

(14) Kim, Y.-J.; Bernstein, M. P.; Galiano-Roth, A. S.; Romesberg, F. E.; Williard, P. G.; Fuller, D. J.; Harrison, A. T.; Collum, D. B. *J. Org. Chem.* **1991**, *56*, 4435.

(15) For extensive references to the chemistry of lithium amide open dimers, see ref 8.

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(18) The relative pK_A's of carbon acids and amines have been studied previously: Fraser, R. R.; Mansour, T. S. *J. Org. Chem.* **1984**, *49*, 3442. Chevrot, C.; Perichon, J. *Bull. Soc. Chem. Fr.* **1977**, 421. Bordwell, F. G.; Bartmess, J. E.; Drucker, G. E.; Margolin, Z.; Matthews, W. S. *J. Am. Chem. Soc.* **1975**, *97*, 3226. Streitwieser, A., Jr.; Ciula, J. C.; Krom, J. A.; Thiele, G. *J. Org. Chem.* **1991**, *56*, 1074. Streitwieser, A., Jr. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1980; Chapter 7. Ahlbrecht, H.; Schneider, G. *Tetrahedron* **1986**, *42*, 4729. Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7068. Fraser, R. R.; Mansour, T. S. *Tetrahedron Lett.* **1986**, *27*, 331. Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7068. Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232. Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 7790.

(19) Fraenkel, G.; Martin, K. V. *J. Am. Chem. Soc.* **1995**, *117*, 10336.

$$\mathbf{5} + \text{PMDTA} \underset{}{\overset{K_{eq}}{\rightleftharpoons}} \mathbf{6} + \text{TMCDA} \qquad (3)$$

oligomer that we believe to be open dimer **7** in rapid degenerate exchange.[20] Addition of 2.0 equiv of PMDTA affords **6** and **7** in a 6:1 molar ratio. Monomer **6** is readily characterized by a ^{6}Li doublet (δ 1.58 ppm, $^1J_{Li-N} = 8.7$ Hz) and ^{15}N triplet (δ 90.0 ppm, $^1J_{Li-N} = 8.6$ Hz). Dimer **7** manifests a very broad ^{6}Li triplet at −50 °C (δ 2.16 ppm, $^1J_{Li-N} = 5.1$ Hz). Dropping the probe temperature causes further broadening of the resonance consistent with a coalescence, but the slow exchange limit showing two discrete lithiums of **7** could not be obtained.[21] The partial solvation (<1.0 solvent per Li) is inferred from the disappearance of **7** at higher [PMDTA].

We concluded the structural studies by determining the relative binding constants of PMDTA and TMCDA to the LDA monomer. Competition of 2.0 equiv of PMDTA and 2.0 equiv of TMCDA in toluene at −80 °C afforded a 1:9 mixture of monomers **5** and **6** (eq 3) corresponding to $K_{eq} = 16$ and $\Delta G° = 1.1$ kcal/mol (±10%). This is similar to the 1.5 kcal/mol preference of PMDTA for the lithium hexamethyldisilazide (LiHMDS) monomer.[7]

Rate Studies. (a) General. We extended previously reported rate studies of the LDA-mediated dehydrobrominations of (±)-2-*exo*-bromonorbornane (**1**, eq 1)[10] to include LDA coordinated by TMEDA, TMCDA, and PMDTA. The LDA used to prepare stock solutions was isolated and recrystallized.[14] The LDA concentrations (0.025−0.40 M) were maintained high relative to **1** (0.004 M) to ensure pseudo-first-order conditions. These conditions also precluded formation of substantial concentrations of mixed aggregates arising from incorporation of the LiBr byproduct.[22] The ligand concentrations were adjusted by using hydrocarbon cosolvent. The rates were monitored via GC analysis of quenched aliquots following the decrease of **1** relative to an internal undecane standard.[10] The decay of **1** displayed first-order behavior over >3 half-lives for all LDA−ligand combinations. Substantial kinetic isotope effects ($k_{obsd(H)}/k_{obsd(D)} = 1.8-4.1$) determined by comparing **1** with the 3,3-dideuterio analogue (**1-*d*$_2$**)[23] confirmed a rate-limiting proton abstraction in all instances.

$$k_{obsd} = k'[\text{LDA}]^n \qquad (4)$$

(b) LDA/TMEDA. Plots of the pseudo-first-order rate constant (k_{obsd}) vs [TMEDA] in hexane are shown in Figure 2. At high [TMEDA] and low temperature (−40 °C), a zeroth-order TMEDA dependence is apparent. A rate maximum at 0.75 equiv of TMEDA in conjunction with no measurable rate in the absence of TMEDA attests to a mechanism with a transition structure bearing a lower TMEDA:lithium ratio than the reactants (<1.0 equiv of TMEDA per Li). Dehydrohalogenations at −20 and 0 °C display more gradual saturation behavior. (Alkyl chloride **2** was employed at 0 °C to maintain observable rates.) Determinations of the reaction order in LDA at several TMEDA concentrations and temperatures afforded

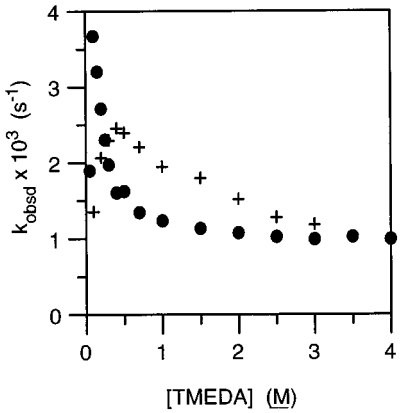


Figure 2. Plot of k_{obsd} vs [TMEDA] in toluene cosolvent for the elimination of (±)-*exo*-2-halonorbornane (0.004 M) by LDA (0.10 M). The (+) symbol represents data obtained at 0 °C with (±)-*exo*-2-chloronorbornane and the (●) symbol represents data obtained at −40 °C with (±)-*exo*-2-bromonorbornane.

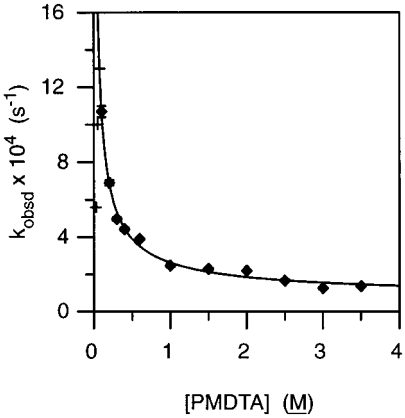


Figure 3. Plot of k_{obsd} vs [PMDTA] in hexanes cosolvent for the elimination of (±)-*exo*-2-bromonorbornane (0.004 M) by LDA (0.10 M) at −40 °C. The (+) symbol represents data that were not included in the fit.

LDA orders in the range 0.65−0.85. Further deconvolution of the rate data for the LDA/TMEDA-mediated dehydrohalogenation proved difficult due to the temperature-dependent desolvation of LDA dimer **4** noted previously.[10] Fortunately, rate studies with LDA/TMCDA and LDA/PMDTA provide a clearer mechanistic picture.

(c) LDA/PMDTA. A plot of k_{obsd} vs [PMDTA] for the LDA−mediated elimination of **1** is illustrated in Figure 3. The zeroth-order PMDTA dependence at high [PMDTA]—conditions affording monomer **6**—attests to an elimination mechanism requiring one PMDTA per Li in the transition structure. A plot of k_{obsd} vs [LDA] in 3.0 M PMDTA (Figure 4) with least-squares fit to eq 4 affords an LDA order of 1.02 ± 0.03 consistent with a monomeric LDA fragment in the rate-limiting transition structure (eq 5).

$$\underset{\mathbf{6}}{i\text{-Pr}_2\text{NLi·PMDTA}} + \mathbf{1} \longrightarrow [i\text{-Pr}_2\text{NLi·PMDTA·}\mathbf{1}]^{\neq} \longrightarrow \mathbf{3} \qquad (5)$$

At low [PMDTA] we observe an approximate inverse-first-order PMDTA dependence,[24] consistent with a second pathway requiring a desolvation. Monitoring k_{obsd} vs [LDA] with 2.0 equiv of PMDTA in hexane (1.0 equiv of uncoordinated

(20) The degenerate site exchange of lithium amide open dimers has been most carefully investigated for TMEDA-solvated lithium 2,2,4,6,6-pentamethylpiperidide.[9]

(21) We generally find that lithium amide and other organolithium dynamic exchange processes observable by NMR spectroscopy are considerably faster in hexane than in toluene.

(22) For an extensive bibliography and leading references to lithium amide mixed aggregation, see: Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9198.

(23) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159. Creary, X.; Hatoum, H. N.; Barton, A.; Aldridge, T. E. *J. Org. Chem.* **1992**, *57*, 1887. Bartsch, R. A.; Lee, J. G. *J. Org. Chem.* **1991**, *56*, 212.

(24) A fit of k_{obsd} vs [PMDTA] (0.1−3.5 M) to the expression $k_{obsd} = k' + k''[\text{PMDTA}]^n$ affords $n = -0.74 \pm 0.06$. (See Figure 3.)

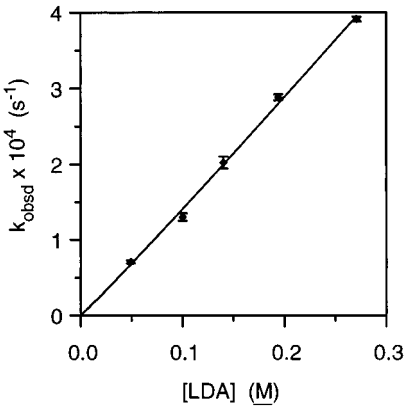


Figure 4. Plot of k_{obsd} vs [LDA] in 3.0 M PMDTA with hexanes cosolvent for the LDA-mediated elimination of (±)-*exo*-2-bromonorbornane (0.004 M) at −40 °C.

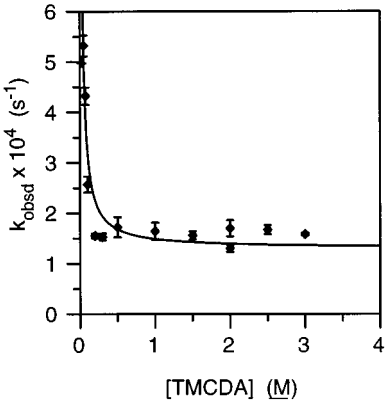


Figure 5. Plot of k_{obsd} vs [TMCDA] in toluene cosolvent for the elimination of (±)-*exo*-2-bromonorbornane (0.004 M) by LDA (0.10 M) at −40 °C.

PMDTA) affords an LDA order of 1.22 ± 0.12. Under these conditions LDA exists as a mixture of monomer **6** and up to 15% open dimer **7**. The isotope effects determined by measuring the reaction rates for **1** and **1-*d*$_2$** are $k_H/k_D = 1.8 \pm 0.2$ at both 0.10 M and 3.0 M PMDTA.

The dehydrohalogenations display measurably different rates in toluene than in hexane. The maximum k_{obsd} at <1.0 equiv of PMDTA is substantially less pronounced in toluene, and the saturation behavior is more readily established. The reaction rates at high [PMDTA] are approximately 3 times faster in hexane. The detectable formation of benzyllithium **8** (see above) does not appear to accelerate the elimination, consistent with the greater kinetic basicity of amides relative to alkyllithiums.[25]

(d) LDA/TMCDA. A plot of k_{obsd} for the LDA/TMCDA-mediated elimination of **1** as a function of [TMCDA] (Figure 5) is qualitatively similar to that observed for LDA/PMDTA. The zeroth-order TMCDA dependence and first-order LDA dependence (1.10 ± 0.10 at 2.0 M TMCDA; Figure 6) implicate a transition structure based upon a monosolvated LDA monomer. The isotope effect determined by measuring the reaction rates for **1** and **1-*d*$_2$** at 2.0 M TMCDA is $k_H/k_D = 3.3 \pm 0.3$, confirming the rate limiting proton transfer. A maximum in the rate at low [TMCDA] is qualitatively consistent with a second mechanism requiring a desolvation.

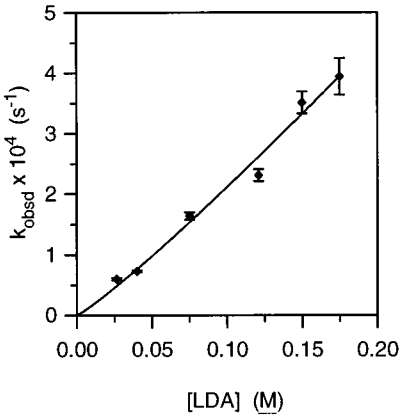


Figure 6. Plot of k_{obsd} vs [LDA] in 2.0 M TMCDA with toluene cosolvent for the LDA-mediated elimination of (±)-*exo*-2-bromonorbornane (0.004 M) at −40 °C.

Discussion

LDA−Polyamine Solution Structures. NMR spectroscopic investigations described previously[5] and those described herein reveal the structure of LDA−ligand complexes to be highly dependent upon the ligand and its concentration. For example, TMEDA affords exclusively disolvated dimer **4**. The TMEDA ligands on **4** are weakly coordinating, displaying an appreciable tendency to dissociate near ambient temperatures to afford a mixture of unsolvated cyclic oligomers. TMCDA shows a substantially higher affinity for LDA, affording exclusively monomer **5** at all TMCDA concentrations.[8] PMDTA affords monomer **6** at >1.0 equiv per Li and predominantly open dimer **7** when only 0.5 equiv of PMDTA per Li is added.

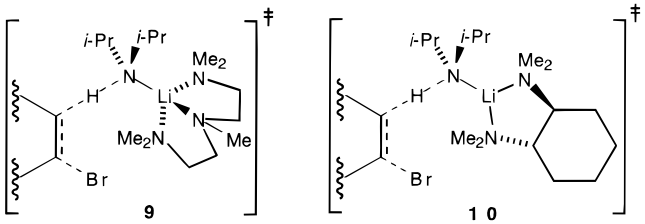
The spectroscopic investigations of LDA/PMDTA mixtures revealed interesting hydrocarbon cosolvent effects. While open dimer **7** is observable at 0.5 equiv of PMDTA in toluene, monomer **6** becomes the exclusive form at ≥1.0 equiv. Similar behaviors were observed when cumene and mesitylene are used. In contrast, limited concentrations of open dimer **7** persist well beyond 1.0 equiv of PMDTA when hexane is employed. Pronounced stabilizations of lithium amide monomers by toluene and related aromatic hydrocarbons[7−9,26] have been tentatively ascribed to the large solvent quadrupoles.[27] The hydrocarbon cosolvents also influence reactivity (see below).

A second consequence of using toluene as the cosolvent is the appearance of appreciable concentrations of PMDTA-solvated benzyllithium **8** (eq 2). Toluene is *not* metalated by LDA in the presence of TMCDA, TMEDA, or a host of other polydentate ligands.[8] The formation of **8** from LDA/PMDTA is interesting given that pK_A measurements suggest such a metalation to be endothermic by as much as 6.0 kcal/mol.[18] Although the literature pK_A's were measured in THF or DMSO solutions, one might assume that solvation effects on the two lithium salts would largely cancel. Clearly, this is not correct. PMDTA is a good ligand for LDA relative to TMEDA, TMCDA, and related polydentate ligands. It would appear, therefore, that PMDTA imparts a disproportionately large stabilization to benzyllithium **8**.

LDA-Mediated Dehydrohalogenations: Monomer- vs Dimer-Based Mechanisms. Rate studies of the dehydrohalogenation of (±)-2-*exo*-bromonorbornane (**1**, eq 1) revealed mechanistic similarities for LDA/TMEDA, LDA/TMCDA, and LDA/PMDTA. Although the facile desolvation of TMEDA-

(25) Trecourt, F.; Mallet, M.; Marsais, F.; Queguiner, G. *J. Org. Chem.* **1988**, *53*, 1367. Veracini, S.; Gau, G. *Nouv. J. Chim.* **1977**, *1*, 419.
(26) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 2217.
(27) Kumpf, R. A.; Dougherty, D. A. *Science* **1993**, *261*, 1708. Dougherty, D. A. *Science* **1996**, *271*, 163. We thank Professor Dougherty for helpful discussions.

solvated dimer **4**[13] precluded a detailed rate study, the other two ligands proved more mechanistically tractable. At elevated ligand concentrations, the elimination rates are independent of ligand concentration and linearly dependent on the LDA concentrations, consistent with rate-limiting transition structures such as **9** and **10** containing monosolvated monomeric LDA fragments. Similar results were obtained with LDA solvated by vicinal amino ethers.[10]



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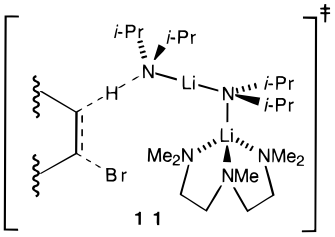

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We feel that the high elimination rates at low ligand concentrations support the hypothesis first put forth by Schlosser and co-workers that dehydrohalogenations can proceed via open dimers.[11] The complete absence of elimination when no ligand is added indicates that solvation is required at the rate limiting transition structure. The rate maxima at <1.0 equiv of ligand per Li (or, in other words, the inverse dependencies of the rates on the ligand concentrations) implicate rate limiting transition structures containing <1.0 equiv of ligand per Li. We infer, therefore, that the rate limiting transition structures contain 0.5 equiv of ligand per Li. Bolstered by spectroscopically observable open dimer **7**, we reiterate Schlosser's hypothesis by invoking open dimer transition structures such as **11**. Evidence implicating the importance of open dimers has been accumulating rapidly.[15] Whether the bromide ion interacts with one of the two lithiums is not obvious.[28] Interestingly, investigations of the dehydrohalogenation with LDA solvated by vicinal amino ethers ($MeOCH_2CH_2NR_2$) did not provide evidence of such a dimer-based mechanism.[10]

Influence of Solvation and Aggregation on Reactivity. Precisely how solvation and aggregation influence organolithium reactivity is poorly understood. For example, a perennial issue is whether monomers or aggregates are more reactive. From a simplistic thermochemical perspective, the least stable reactant should be the most reactive. Consequently, forcing the formation of monomers by adding monomer-stabilizing ligands should attenuate their reactivity. Indeed, the relative reaction rates via the monomer pathway (at 3.0 M ligand concentration) are as follows: TMEDA, 1.0; TMCDA 0.17; PMDTA, 0.19. *The highest reactivity is observed for the ligand that affords dimeric rather than monomeric LDA in the ground state.* Furthermore, the approximate 1.0 kcal/mol difference in binding of PMDTA and TMCDA is not reflected in the nearly equal elimination rates, suggesting that ground state and transition state solvation effects cancel.[29]

Which pathway affords the highest reaction rates under optimal conditions? Conventional wisdom seems to suggest that optimum rates will be obtained by adding strong ligands to promote the monomer-based pathway. In this particular rate study, the maximum rates are obtained by promoting the putative dimer-based pathway at low concentrations of the inferior ligand. Similar conclusions were drawn from rate studies of LDA-mediated imine metalations.[30]

Some comment on the role of the hydrocarbon cosolvent is warranted. In several investigations we have noted a surprising stabilization of lithium amide monomers by toluene and related aromatic hydrocarbons *even in the presence of excess donor ligands.*[7−9,26] For instance, monomer **6** was found to be stabilized relative to open dimer **7** in toluene compared to hexane. However, toluene also causes a measurable (up to 3-fold) *suppression* of both the monomer- and dimer-based eliminations when compared to hexane. While the rate inhibitions are not large, we feel they are remarkable for a change from one lipophilic cosolvent to another. Beak reported 5-fold changes in the absolute stereocontrol for a reaction of alkyllithium/sparteine complexes by simply substituting toluene for hexane.[31] What makes aromatic solvents so special? As noted by Dougherty,[27] the large quadrupoles of benzenoids may be important. Exactly how the highly quadrupolar aromatic solvents influence organolithium structure and reactivity remains unclear and an important issue.

Summary and Conclusions

Investigations of the structure and reactivity of polyamine-solvated LDA led to the following general observations and conclusions:

1. Treatment of LDA with excess TMEDA, TMCDA, and PMDTA affords (respectively) dimer **4**, monomer **5**, and monomer **6**. Treatment of LDA with <1.0 equiv of PMDTA affords substantial concentrations of open dimer **7**, while TMEDA and TMCDA afford **4** and **5** (respectively) along with unsolvated oligomers. Toluene and several other aromatic hydrocarbons appear to stabilize PMDTA-solvated monomer **6** relative to open dimer **7** as found in previous investigations of amine-solvated lithium amides.

2. Toluene solutions of LDA/PMDTA show appreciable concentrations of PMDTA-solvated benzyllithium **8** in equilibrium with monomer **6**, despite pK_A measurements in other solvents suggesting the metalation of toluene by LDA to be highly endothermic. The solvent-dependent relative acidities of diisopropylamine and toluene are ascribed to an unusually high stabilization of benzyllithium by PMDTA. The results highlight the limitations of extrapolating pK_A's from one solvent to another.

3. Rate studies of LDA-mediated dehydrohalogenations (eq 1) reveal qualitatively similar behavior for three polyamines. At high ligand concentrations, the eliminations are found to proceed via transition structures based upon monosolvated monomers (e.g., **9** and **10**) akin to those noted in related rate studies.[10] At low ligand concentrations, more efficient pathways suggested to involve lithium amide open dimers (e.g., **11**)

(28) We investigated the stereochemistry of the elimination using (±)-3-exo-deuterio-2-*exo*-bromonorbornane as described previously.[10] However, all ligands and ligand concentrations afforded approximately 70−80% syn-exo elimination, affording little mechanistic insight.

(29) There are a number of reports where ostensibly weaker solvent−lithium interactions lead to increased overall reaction rates. For an extensive bibliography, see ref 10.

(30) Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 789. Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 8008.
(31) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715.
(32) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.
(33) Hall, P.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575.

dominate. Detection of the dimer-based pathway supports a proposed elimination mechanism proffered by Schlosser and co-workers.[11]

4. While higher organolithium reactivities are often associated with strongly coordinating polydentate ligands and accompanying deaggregations, the studies described herein reveal optimal rates from the putative dimer-based pathways.

Experimental Section

Reagents and Solvents. All amines and hydrocarbons were distilled by vacuum transfer from blue or purple solutions containing sodium benzophenone ketyl. The hydrocarbon stills contained 1% tetraglyme to dissolve the ketyl. ^{6}Li metal (95.5% enriched) was obtained from Oak Ridge National Laboratory. The [^{6}Li]ethyllithium used to prepare the [^{6}Li,^{15}N]LDA was prepared and purified by the standard literature procedure.[14] [^{6}Li,^{15}N]LDA was prepared and isolated as an analytically pure solid as described previously.[14] The diphenylacetic acid used to check solution titers[32] was recrystallized from methanol and sublimed at 120 °C under full vacuum. Air- and moisture-sensitive materials were manipulated under argon or nitrogen with use of standard glovebox, vacuum line, and syringe techniques.

NMR Spectroscopic Analyses. Samples for spectroscopic analyses were prepared by using a sample preparation protocol described in detail elsewhere.[33] Standard ^{6}Li, ^{15}N, and ^{13}C NMR spectra were recorded on a Varian XL-400 spectrometer operating at 58.84, 40.52, and 100.58 MHz (respectively) or on a Varian Unity 500 spectrometer operating at 73.57, 58.84, and 125.76 MHz (respectively). The ^{6}Li, ^{15}N, and ^{13}C resonances are referenced to 0.3 M [^{6}Li]LiCl/MeOH at −100 °C (0.0 ppm), neat Me_2NEt at −100 °C (25.7 ppm), and the toluene methyl resonance at −100 °C (20.4 ppm), respectively.

Kinetics. For a kinetic run corresponding to a single rate constant, a relatively concentrated (0.5−0.8 M) stock solution of LDA in a ligand−toluene solution was prepared and titrated to determine the precise concentration. The solution was diluted to a concentration appropriate for the particular series and titrated a second time. A series of oven-dried, nitrogen-flushed 5 mL serum vials (5−10 per rate constant) fitted with stir bars were charged with the LDA stock solution and brought to the desired temperature (± 0.2 °C) with use of a constant-temperature bath fitted with a National Bureau of Standards thermometer. The (±)-2-*exo*-bromonorbornane was added as a 0.047 M stock solution in the appropriate ligand−toluene mixture containing undecane (0.047 M) as a GC standard. The vessels were periodically quenched with 1:1 H_2O−THF at intervals chosen to ensure an adequate sampling of each of the first three half-lives. The quenched aliquots were extracted into Et_2O, and the extracts were analyzed via capillary GC. Analysis using Hewlett-Packard GC fitted with an autoinjector and a 60 m DB-5 column (J & W Scientific) provided excellent reproducibility. The eliminations were monitored by following the decrease of the (±)-2-*exo*-bromonorbornane (**1**) relative to the internal undecane standard. Following the formation of the norbornene afforded equivalent rate constants (±10%). Rate constants were determined by numerical integration with a convergence protocol using the Scientist distributed by MicroMath. Nonlinear least-squares fits to the integral form of the rate laws afforded numerically indistinguishable results. The reported errors correspond to one standard deviation. The observed rate constants were shown to be reproducible within ±5%.

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Supporting Information Available: ^{6}Li and ^{15}N NMR spectra of LDA/PMDTA and rate data for the dehydrohalogenations (17 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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